REMARKS

Entry of the amendment and reconsideration of the claims in view of the following Remarks is requested.

Claim 23 has been amended for clarity. The amendment is supported throughout the specification including at page 10, lines 30-35.No new matter is added by the amendment. Claims 1-3, 7-12, and 20-23 are pending in the application.

35 U.S.C. §112, first paragraph

Claims 1-3, 7-12, and 20-23 were rejected under 35 U.S.C. 112 for lack of written description. Applicants respectfully traverse this rejection.

As an initial matter, Applicants note there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. See *Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA.* Furthermore, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to practice, by disclosure of relevant identifying characteristics such as structure, physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of these characteristics. *MPEP 2163 II. A.3.(a)ii).* When the above factors are carefully weighed, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the claimed invention.

Independent claims 1, 20, and 23 are directed to isolated libraries of structurally-constrained cyclic peptides (claims 1 and 23), or an isolated plurality of cyclic peptides having a reverse turn secondary structure (claim 20), wherein the cyclic peptide comprises an amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2. The Examiner has several bases for the rejection: 1) the Examiner contends that the disclosure does not adequately describe the genus represented by position A3 of the claimed peptides and 2)the Examiner contends that the specification does not describe the length , kind, or combination of residues of A3. Applicants respectfully disagree.

Applicants submit that one of skill in the art reading the specification would understand that Applicants were is possession of the claimed library of cyclic peptides. Applicants have

described the structure of the claimed peptides including that of the A3 position. Applicants have described that the A3 position can include up to 12 amino acids and can be any naturally occurring amino acid. In a specific embodiment, Applicants have demonstrated the preparation of a library of cyclic peptides comprising CX8C as well as XCTWX4LTCX, wherein X4 is any naturally occurring amino acid. See the specification atpage 23, Example 1 and page 35, Example 5. Applicants have further described many specific embodiments at page 29 in the specification. Applicants have shown and described that different turn sequences having different amino acid sequences can be presented as cyclic peptides as claimed. Therefore, Applicants have described the structure of the claimed cyclic peptides, many species of the claimed cyclic peptides, and provide an actual reduction to practice.

Furthermore, the Applicants have in fact disclosed and exemplified a representative number of species within the claimed genus. The disclosure specifically exemplifies a scaffold shown to stabilize the turn sequence EGNK (Example 1), the C'-C" hairpin loop (residues 37-46) of the CD4 region of HIV gp120 (Example 2), the turn sequence ENGK, the turn sequence QGSF the turn sequence KGNE; the turn sequence VWQL from the F-G loop of domain 2 of human Fc-epsilon-RI (Example 2), and the turn sequence GPLT from the EPO agonist peptide EMP1 (Example 2). Indeed, the specification discloses that some of these sequences are "difficult" turns, yet were successfully stabilized by the claimed peptide scaffold (page 29, lines 10-12). Therefore, Applicants submit that the specification discloses a representative number of species of the genus of A3.

The Examiner also asserts that the specification provides no specific description of a cyclic peptide having additional residues at the N or C terminus. The Examiner contends that the effect of these additional residues on the stability of the peptide is unpredictable, since the present Examples indicate that a change in one amino acid can result in a conformationally unstable peptide. Applicants disagree, and respectfully request that the Examiner specifically indicate where this result is allegedly shown. Applicants submit that the Examples show that turn sequences are in fact stably presented in the claimed cyclic peptides (See, for example, Table 2). Applicants submit that the Examiner has provided no any evidence that the presence of additional residues on either end of the claimed peptides would cause conformational instability.

For the reasons discussed above, the specification clearly demonstrates the ability of the claimed cyclic peptides to stabilize a variety of different types of β-turn sequences having widely varying amino acid sequences. The Examiner has provided no evidence showing that the claimed cyclic peptides would not be effective in stabilizing other turn sequences within the scope of the claimed A3 genus, or that Applicants have not disclosed a representative number of species of the claimed A3 genus.

The Examiner also states that the disclosure of one species does not necessarily describe a genus, and asserts that only three species are disclosed in the present specification. As discussed above, however, Applicants have disclosed multiple species of turn sequences that differ in amino acid sequence. Therefore, Applicants submit that the specification adequately describe the cyclic peptides as claimed.

For the foregoing reasons, Applicants submit that the Examiner has not overcome the strong presumption of adequate written description, and that claims 1-3, 7-10, and 20-23 are fully described by the specification. Withdrawal of the rejection is therefore requested.

35 U.S.C. §103 (a)

The Examiner rejected claims 1-3, 7-10, and 20-23 under 35 U.S.C. § 103(a) as obvious over Wrighton et al. (U.S. Pat. No. 5,830,851). The Examiner asserts that the peptide libraries of Wrighton et al. render the claimed library *prima facie* obvious, for reasons advanced in the previous Office Action. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: (1) the reference must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art to modify the reference to obtain all of the claim limitations; and (3) there must be a reasonable expectation of success. Applicants submit that not all of these requirements have been met, because the reference does not disclose all of the claim limitations, there is no suggestion or motivation to modify the reference to disclose all of the claim limitations, and there would not have been a reasonable expectation of success in doing so.

Independent claims 1, 20, and 23 are directed to isolated libraries of structurally-constrained cyclic peptides (claims 1 and 23), or an isolated plurality of cyclic peptides having a

reverse turn secondary structure (claim 20), wherein the cyclic peptide comprises an amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2, wherein A2 and A4 are W (claim 23), or A2 is 2 and A4 is W or L (claims 1 and 20). Applicants submit that Wrighton et al. does not disclose any cyclic peptides within the scope of the claims. Moreover, in the preferred embodiments disclosed in Wrighton et al., X5 of Wrighton et al., which corresponds to A2 of Applicants' claims, is limited to M, F, or I. Therefore this reference does not disclose all of the elements of the claims.

Applicants submit that the Examiner has not established that one of skill in the art would have been motivated to modify the peptides of Wrighton et al to obtain the peptides as claimed by Applicants. The present invention is directed to cyclic peptides. The cyclic peptides can present secondary structures, such as a ß-turn hairpin structure. Applicants have discovered that cyclic peptides as claimed are useful in stabilizing ß-turn structures.

In contrast, and as stated in Applicants' previous Response, Wrighton et al., is directed to identifying agonists of EPO. The Wrighton et al reference is concerned with solving a different problem than that of the Applicants. Wrighton et al. nowhere teaches or suggests the desirability of forming a trp-trp or trp-leu cross-strand pair between A2 and A4 of the claimed peptides, as a means of enhancing hairpin stability. Wrighton et al. does not teach or suggest the ability of the presently claimed cyclic peptides to accommodate a number of different types of turn structures, or that the stability of the turn sequences would be enhanced by using a cyclic peptide having the presently claimed residues. Indeed, Wrighton et al. fails to teach or suggest the desirability of a peptide that can stabilize a ß-turn structure, or even that any peptide can stabilize a ß-turn structure. Wrighton et al.'s failure to teach any properties or uses of the disclosed peptides that are similar to those of the presently claimed peptides is evidence of nonobviousness.

Indeed, and as stated in the previous Response, the preferred embodiments disclosed by Wrighton et al. actually teach away from the presently claimed subgenus. Wrighton et al. specifies that the preferred embodiments have an M, F, or I at the position corresponding to A2. The disclosure of these preferred embodiments would lead one of skill in the art to make different substitutions at this position than those claimed by Applicants, providing further evidence of nonobviousness. In response to Applicants' arguments regarding preferred embodiments, the Examiner states that disclosure of a preferred embodiment does not preclude other teachings of the prior art. Nevertheless, the existence of structural dissimilarities between

Applicants' claimed peptides and the preferred embodiments of the cited reference is evidence of nonobviousness that the Examiner must consider.

The Examiner also asserts that the Applicants apparently contradict themselves, by stating that Wrighton et al. is directed to identifying EPO agonists, while also allegedly contending that Wrighton et al. does not teach identifying species that are agonists of EPO, or that present ß-turn structures, or for any other reason. The Applicants respectfully disagree with the Examiner's characterization of Applicants' remarks. The Applicants have not disputed that Wrighton et al. is directed to identifying species that are agonists of EPO. Rather, Applicants contend that Wrighton et al. fails to teach or suggest the library of peptides as claimed by Applicants.

The Examiner also contends that arguments based upon the failure of Wrighton et al. to teach peptides that stabilize a ß-turn structure are not commensurate in scope with any claims not reciting this property. The Applicants respectfully disagree with the Examiner's contention. As stated above, the Examiner must provide a motivation to modify the peptides of Wrighton et al., regardless of whether or not the motivation relates to a property recited in Applicants' claims. Applicants submit that they have provided evidence that Wrighton et al. does not provide any such motivation, in the least because Wrighton et al does not teach or suggest that peptides can stabilize beta turn sequences.

Applicants respectfully submit that the Examiner has not identified a single peptide disclosed by Wrighton et al. that falls within the scope of the claims. Rather, the Examiner has alleged the existence of a motivation to modify Wrighton et al. to obtain a species of Applicants' subgenus, by pointing to specific residues of certain Wrighton et al. species (i.e., SEQ ID NOs 86 and 89) that themselves clearly fall outside the present claim scope. The Examiner alleges that Wrighton et al. discloses generally that any natural amino acid can be used at a position corresponding to A2 of the present claims. The Examiner concludes, therefore, that it would have been within the ordinary skill in the art to use a Trp at position A2. Specifically, the Examiner points to Wrighton et al.'s disclosure of peptides said to contain a Trp at A2, such as SEQ ID 86 and SEQ ID 89.

Applicants respectfully disagree. As discussed above, the present claims are limited not merely by the amino acid at position A2, but also recite that the amino acids at positions A1 and

A5 are W, Y, F, H, V, T, or I. SEQ ID 89, however, has the amino acid E at the position corresponding to A1 of the present claims and SEQ ID NO:86 has the amino acid Q at position A1 and amino acid L at position A5. Applicants submit, therefore, that a peptide with the sequence of SEQ ID 89 or SEQ ID NO:86 is not a species falling within the present claims.

Applicants respectfully submit that the Examiner is combining residues from different peptides of Wrighton et al. to obtain a species falling within the present claims, but without any motivation or reasonable expectation of success, other than that provided by the Applicants' own specification. The Examiner is reminded that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *MPEP 2142*. Applicants submit that only the present specification, and not the prior art, provides the teaching that the claimed peptides are useful in stabilizing ß-turn structures.

The Examiner additionally asserts, however, that the specific peptides disclosed by Wrighton et al. show that the various positions can have any of the 20 naturally occurring amino acids, such that it is expected that each position of the Wrighton et al. peptides can have the amino acid of the corresponding position of the presently claimed peptides. The Examiner concludes, therefore, that one of ordinary skill would be motivated to substitute the A2 position with every natural amino acid, including W, to facilitate identification of lead compounds. Applicants disagree.

The mere assertion in the prior art that a given position can be "any amino acid" does not provide a motivation to modify a peptide to a particular amino acid at that position. As stated in Applicants' previous Response, the Examiner's reasoning represents an improper "obvious to try" rationale for modifying the prior art reference. Both a motivation to modify the peptides of the cited reference, and a reasonable expectation of success, must exist to support a *prima facie* case of obviousness. A mere assertion that a position can be varied, and that it would be beneficial to vary the position until a successful result is achieved, represents an improper "obvious to try" rationale, and does not supply the necessary motivation to modify the prior art. *MPEP 2145(X)(B)*. "An invention is "obvious to try" where the prior art [gives] either no indication of which parameters [are]critical or no direction as to which of many possible choices is likely to be

successful." In re O'Farrell, 853 F. 2d 894, 903, 7USPQ 2d 1673, 1681 (Fed. Cir.1988) Applicants submit that the Examiner has not shown that Wrighton et al provides such guidance.

The Examiner states that the present rejection does not rely on an "obvious to try" rationale, because Wrighton et al. discloses specific species in addition to a generic library, and because the case law holds that the selection of a certain combination of compounds from among thousands of compounds disclosed by the prior art, does not render claims directed to the selected combination nonobvious (*Merck & Co. Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ 2d 1843 (Fed. Cir. 1989)). The Applicants disagree with the Examiner's conclusion.

Applicants respectfully submit that *Merck* is inapplicable to the present claims, because the issue in *Merck* revolved around combinations of compounds, and not upon the modifications of those compounds. The prior art in *Merck* was directed to compositions comprising the combination of two compounds selected from two classes of compounds known to be useful as diuretics. The holding in *Merck* merely states that the prior art rendered obvious claims directed to compositions comprising a specific compound from each of the classes of compounds disclosed by the prior art.

Applicants submit that claims 1-2, 4-5, and 8-9 are patentable over Wrighton et al., at least for the foregoing reasons. Withdrawal of the rejection is therefore requested.

Double Patenting

The Applicants acknowledge the provisional rejection of claims 1-3, 7-12, and 20-23 under the judicially created doctrine of obviousness-type double patenting over claims 1-5, 7, 9-11, 13, and 18-25 of copending Application No. 10/271,343. The Applicants will consider whether to file a terminal disclaimer, if appropriate, upon indication of allowable claims.

Request for an Interview

Applicants request an interview with the Examiner and her supervisor. Applicants request that the Examiner contact Applicants representative to schedule the interview upon receipt of these papers.

SUMMARY

Applicants submit that all pending claims are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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